Paul

Access DB# 66073

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: P. Spivack Examiner #: 70400 Date: 4/30/02
Art Unit: 1614 Phone Number 30 8 4703 Serial Number: 09/995277
Mail Box and Bldg/Room Location: 2D05 Results Format Preferred (circle): PAPER DISK E-MAIL
2D01

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Fc Receptor Modulators

Inventors (please provide full names): Jonathan B. Baell
Thomas P. J. Garrett

Earliest Priority Filing Date: 9/11/98

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search:
methods for inhibiting Fc receptor binding of immunoglobulin comprising administering:
BRI 6728 → 1,2 bis (m-carboxyphenyl) ethane
BRI 6727 - Cl16
BRI 6734
BRI 6814
BRI 6824
BRI 6823
BRI 6822
BRI 6817
BRI 6829
BRI 6855

Thanks

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: Paul Schulwitz	NA Sequence (#)		STN	✓
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Searcher Location:	Structure (#)	2	Questel/Orbit	
Date Searcher Picked Up: 5/6	Bibliographic		Dr.Link	
Date Completed: 5/7	Litigation		Lexis/Nexis	
Searcher Prep & Review Time: 30	Fulltext		Sequence Systems	
Clerical Prep Time:	Patent Family		WWW/Internet	
Online Time:	Other		Other (specify)	

PTO-1590 (8-01)

examination of the following examples thereof, which are not intended to be limiting.

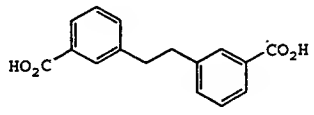
EXPERIMENTAL

The following abbreviations and terms are used herein:

rt	room temperature
Et_2O	diethyl ether (*i.e.*, ether or ethyl ether)
MS (APCI)	atmospheric pressure chemical ionization
THF	Tetrahydrofuran
EtOAc	Ethyl acetate
TMSCl	Trimethylsilyl chloride
CH_3CN	Acetonitrile
DMF	Dimethylformamide

Experiment 1

This experiment illustrates a synthesis of 1,2-Bis(*m*-carboxyphenyl)ethane:



BRI 6728

Step 1: 1,2-Bis(*m*-bromophenyl)ethane was prepared by the method of Lindsay *et al* (JACS, **1961**, *83*, 943) as follows. Magnesium (0.05 g, 2.0 mmol) was added to a solution of 3-bromobenzylbromide (1.0 g, 4.0 mmol) in Et_2O (10 mL) at rt. After

1,2-bis(*m*-carboxyphenyl)ethane as a white solid. MS (APCI) *m/z* 269 (M+1, 100%) ^{13}C NMR (50 MHz, d_6-DMSO): δ 38.4, 128.8, 130.3, 131.1, 132.5, 134.8, 143.5, 169.2. The melting point agreed with that reported by Lindsay *et al* (JACS, 1961, **83**, 943).

Experiment 2

This experiment illustrates a synthesis of

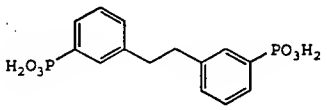
Step 1: A mixture of 3-bromophenol (13.8 g, 80 mmol), 3-bromobenzyl bromide (10 g, 40 mmol), K_2CO_3 (16.6 g: 120 mmol) and NaI (300 mg, 2 mmol) in acetone (100 mL) was heated to reflux for 12 hours. The reaction mixture was cooled to rt, concentrated *in vacuo* and partitioned between Et_2O (300 mL) and water (300 mL). The organic phase was washed with aqueous NaOH (1 M, 300 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 3-[(*m*-bromophenyl)methoxy]bromobenzene as a clear oil. MS (APCI) *m/z* 339 (M^+-3, 50%), 341 (M^+-1, 100%), 343 (M^++3, 50%), ^{13}C NMR (50 MHz, $CDCl_3$); δ 68.9, 113.4, 117.9, 122.5, 122.6, 124.1, 125.6, 129.9, 130.0, 130.4, 130.9, 138.4, 158.9.

Step 2: Using 3-[(*m*-bromophenyl)methoxy]bromobenzene and the

method described in Example 1, step 2 gave 3-[(*m*-carboxyphenyl)methoxy]-benzoic acid as a white solid. MS (APCI) *m/z* 271 (M^+-1, 100%). ^{13}C NMR (50 MHz, d_6-DMSO): δ 68.3, 114.5, 119.3, 121.5, 127.8, 128.3, 129.3, 130.5, 131.5, 131.8, 137.0, 157.7, 166.6, 166.7.

Experiment 3

This experiment illustrates a synthesis of 1,2-bis(3-phosphono-phenyl)ethane:



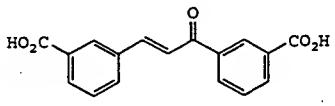
BRI6813

Step 1: 1,2-Bis(3-bromophenyl)ethane (obtained using the method of Example 1, step 1) (440 mg., 1.29 mmol), diethyl phosphite (0.46 mL, 3.59 mL) and triethylamine (0.5 mL, 3.59 mmol) were dissolved in toluene and degassed. $Pd(PPh_3)_4$ (185 mg, 0.16 mmol) was added in one portion and the reaction heated to 90 °C for 16 hours. The reaction was cooled to room temperature and purified by column chromatography (SiO_2, 50% EtOAc in petroleum ether → 100% EtOAc → 100% EtOH) to give 1,2-bis[3-(diethoxyphosphono)phenyl]-ethane as a white solid. MS (APCI) *m/z* 455 (M^++1, 100%). ^{31}P NMR (81MHz, proton decoupled, $CDCl_3$): δ +19.5.

Step 2: Trimethylsilylbromide (1.03 mL, 7.8 mmol) was added dropwise to a solution of the above ester (586 mg, 1.30 mmol) in CH_2Cl_2 (10 mL) at rt. The reaction was stirred for 16 hours at room temperature and concentrated *in vacuo*. MeOH (5 mL) was added and the solution concentrated *in vacuo*. This procedure was repeated a further two times to give 1,2-bis(3-phosphonophenyl)ethane as a white solid. MS (APCI) *m/z*. 341 (M^+-1, 100%). ^{31}P NMR (81MHz, proton decoupled, $CDCl_3$): δ +14.6.

Experiment 4

This experiment illustrates a synthesis of 3,3'-Dicarboxy-chalcone:



BRI 6734

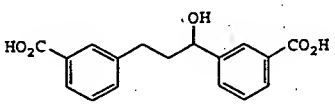
Step 1: 3-Cyanobenzaldehyde (3.0 g, 23.0 mmol) and 3-cyanoacetophenone (3.34 g, 23.0 mmol) in glacial acetic acid (5 mL) and concentrated H_2SO_4 (3.66 mL, 69 mmol) was stirred at room temperature for 72 hours. Water (200 mL) was added and the reaction filtered. The precipitate was washed with water (2 x 200 mL) and dried *in vacuo* to give 3,3'-dicyanochalcone as an off-white solid. MS (APCI) *m/z* 258 (M^+-1, 100%). ^{13}C NMR (50 MHz, d_6-DMSO): δ 111.7, 117.8, 118.0, 123.0, 129.7, 131.6, 132.1, 132.4, 133.3,

133.5, 135.3, 136.1, 137.4, 142.1, 187.3.

Step 2: A solution of 3,3'-dicyanochalcone from step 1 (2.0 g, 7.75 mmol) in glacial acetic acid (30 mL) was treated with a mixture of concentrated H_2SO_4 (10 mL) and water (10 mL). The reaction mixture was heated to 130 °C for 12 hours, cooled to room temperature and filtered. The precipitate was washed with water (3 x 100 mL) and dried *in vacuo* to give 3,3'-dicarboxychalcone as a yellow solid. MS (APCI) *m/z* 295 (M^+-1, 100%). ^{13}C NMR (50 MHz, d_6-DMSO); δ 122.5, 128.6, 128.7, 129.2, 130.8, 131.0, 131.2, 132.4, 132.5, 133.1, 134.5, 137.2, 143.1, 166.3, 166.5, 188.2

Experiment 5

This experiment illustrates a synthesis of 1,3-bis (*m*-carboxyphenyl)-1-propanol:



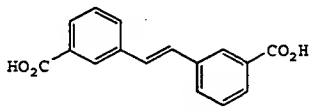
BRI 6814

3,3'-Dicarboxychalcone (Example 4, step 2) (430 mg, 1.45 mmol) in ethanol (10 mL) containing aqueous NaOH (1 M, 2.90 mmol) was hydrogenated at 45 psi for 48 hours in the presence of Wilkinson's catalyst (67 mg, 0.07 mmol). The reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in methanol (10 mL) and treated with $NaBH_4$ (220 mg, 5.8 mmol) at rt. The reaction

mixture was stirred for 16 hours at rt, quenched with the cautious addition of saturated aqueous NH_4Cl and partitioned between EtOAc (50 mL) and aqueous HCl (1 M, 50 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 1,3-bis (*m*-carboxyphenyl)-1-propanol as a viscous oil. MS (APCI) *m/z* 299 (M^+-1, 100%). ^1H NMR (200 MHz, $CDCl_3$); δ 1.95-2.10, m, 2H; 2.68-2.83, m, 2H; 4.62-4.78, m, 1H; 7.03-7.60, m, 4H; 7.75-8.03, m, 4H.

Experiment 6

This experiment illustrates a synthesis of trans-3,3'-bis-carboxystilbene:



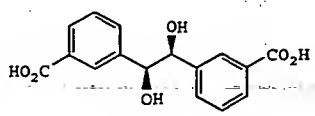
BRI 6824

Step 1: Methyl 3 -bromobenzoate (21.5 g, 100 mmol), $Pd(OAc)_2$ (224 mg, 1 mmol), tri-*o*-tolylphosphine (608 mg, 2 mmol) and tributylamine (26.2 mL, 110 mmol) in DMF (100 mL) was degassed with argon and heated to 130 °C for 6 hours while a stream of ethylene was bubbled through the solution. The reaction mixture was cooled to room temperature and filtered. The precipitated was washed with cold Et_2O (2 x 50 mL) and dried *in vacuo* to give *trans*-3,3'-bis-carboxystilbene dimethyl ester as an off-white solid. ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.2, 127.5, 128.8, 130.6, 130.9, 137.2, 166.9.

Step 2: The above diester (500 mg, 1.7 mmol) in the THF (10 mL) was treated at room temperature with aqueous LiOH (1 M, 10 mL). After stirring for 16 hours at rt, the reaction mixture was partitioned between Et_2O (50 mL) and water (50 mL). The aqueous phase was separated and the organic phase was extracted with water (25 mL). The combined aqueous extracts were acidified with concentrated aqueous (HCl while maintaining the internal temperature below 10 °C. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated *in vacuo* to give *trans*-3,3'-Biscarboxystilbene as a white solid. MS (APCI) *m/z* 267 (M^+-1, 100%). ^1H NMR (200 MHz, d_6-DMSO): δ 7.28-7.56, m, 2H; 7.78-7.90, m, 2H; 8.20, s, 1H.

Experiment 7

This experiment illustrates a synthesis of (S,S)-1,2-bis-(3-carboxyphenyl)ethane-1,2-diol:



BRI 6823

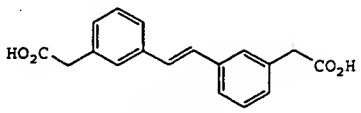
Step 1: *trans*-3,3'-Biscarboxystilbene dimethyl ester (Example 6, step 1) (5.0 g, 16.9 mmol) and N-methylmorpholine-N-oxide (2.2 g, 18.6 mmol) in acetone (50 mL) and water (20 mL) were treated at

room temperature with an aqueous solution of OsO_4 (4.3 mL, 39.4 mM, 0.17 mmol). The reaction mixture was stirred for 16 hours at rt, quenched by addition of sodium metabisulfite (3.0 g) and the pH adjusted to about pH 7 with 2 M aqueous sulfuric acid. The acetone was removed *in vacuo* and the remaining solution acidified to about pH 2, saturated with NaCl and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give (R,R)-1,2-bis-[3-(carbomethoxy)-phenyl]ethane-1,2-diol as a white solid. ^1H NMR (200 MHz, $CDCl_3$): δ 3.2, bs, 1H; 3.82, s, 3H; 4.77, s, 1H; 7.20-7.31, m, 2H; 7.80-7.89, m, 2H.

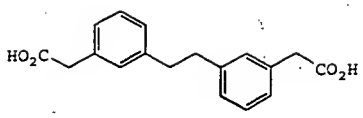
Step 2: The above diester (500 mg, 1.5 mmol) was hydrolyzed using the procedure described in Example 6, step 2 to give (S,S)-1,2-bis-(3-carboxyphenyl)ethane-1,2-diol as a white solid. MS (APCI) *m/z* 301 (M^+-1, 100%). ^1H NMR (200 MHz, d_6-DMSO): δ 3.40, bs, 1H; 4.76, s, 1H; 5.56, bs, 1H; 7.20-7.29, m, 2H; 7.80-7.91, m, 2H.

Experiment 8

This experiment illustrates a synthesis of 3,3'-bis-(carboxy-methyl)stilbene:



BRI 6822



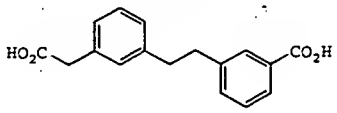
BRI 6817

Step 1: 3,3'-Bis-[(carbomethoxy)methyl]stibene (Example 8, step 1) (500 mg, 1.5 mmol) and palladium on carbon (10%, 200 mg) in methanol (20 mL) was hydrogenated under an atmosphere of hydrogen for 16 hours at rt. The reaction was filtered and concentrated *in vacuo* to give 1,2-bis-[*m*-(carbomethoxymethyl)phenyl]ethane as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.91, s, 2H; 3.63, s, 2H; 3.72, s, 3H; 7.08-7.31, m, 4H.

Step 2: The above ester was hydrolyzed using the procedure described in Example 6, step 2 to give 1,2-bis-]*m*-(carboxymethyl] ethane as a white solid. MS (APCI) *m/z* 297 (M^+-1, 100%). ^{1}H NMR (200 MHz, d_6-DMSO): δ 2.82, s, 2H; 3.56, s, 2H; 7.06-7.06-7.27, m, 4H; 12.25, bs, 1H.

Experiment 10

This experiment illustrates a synthesis of 1-[*m*-(carboxymethyl)phenyl]-2-[*m*-(carboxyhenyl)]ethane:



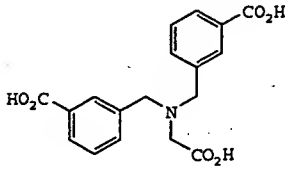
BRI 6829

Step 1: Methyl 3-(ethenyl)phenylacetate (Example 8, step 1)

(M$^+$-1, 100%). ^{1}H NMR (200 MHz, d_6-DMSO): δ 2.92, m, 4H; 3.55, s, 2H; 7.02-7.35, m, 4H; 7.36-7.60, m, 2H; 7.71-7.93, m, 2H. ^{13}C NMR (50 MHz, d_6-DMSO): δ 38.6, 38.7, 40.9, 128.5, 128.8, 130.0, 130.3, 131.0 131.2, 132.6, 134.8, 136.7, 143.1, 143.8, 169.2, 174.5.

Experiment 11

This experiment illustrates a synthesis of N,N-bis(*m*-carboxybenzyl)glycine:



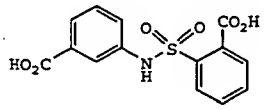
BRI 6815

Step 1: *m*-Cyanobenzyl bromide (2.35 g, 12.0 mmol) was slowly added to a solution of glycine methyl ester hydrochloride (0.63 g, 5.0 mmol), $NaHCO_3$ (1.4 g, 17.0 mmol) and NaI (0.37 g, 2.4 mmol) in DMSO (5 mL) and THF (20 mL). The reaction was heated to reflux for 2 hours, cooled to room temperature and diluted with EtOAc (50ml) and water (40 mL). The organic phase was washed with water (3 x 40 mL), saturated aqueous NaCl (40 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give N,N-Bis(*m*-cyanobenzyl)glycine methyl ester as a colorless oil of sufficient purity for subsequent reactions. Additional purification can be achieved by extraction into dilute aqueous acid, basification and extraction in an organic

FcγRIIa with IgG1 (Figures 6 and 8). Compounds BRI6728, BRI6734, BRI6813, BRI6800, BRI6801, BRI6802, BRI6803, BRI6814, BRI6816, BRI6817, BRI6822, BRI6823 and BRI6824 inhibited the interaction of soluble FcγRIIa with IgG3 (Figures 7 and 9). Compounds BRI6727, BRI6798, BRI6815 and BRI6825 all enhanced the interaction between soluble FcγRIIa with IgG3 at concentration of about 5 mg/mL and 10 mg/mL.

Experiment 15

This experiment illustrates a synthesis of N-(3'-carboxyphenyl)-2-(carboxybenzene)sulfonamide:



BRI 6855

Step 1: Methyl 2-(chlorosulfonyl)-benzoate (2.25 g, 8.73 mmol) in methylene chloride (20 mL) was added dropwise to a solution of ethyl 3-aminobenzoate (1.44 g, 8.73 mmol) and triethylamine (1.21 mL, 8.73 mmol) in methylene chloride (10 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with water (20 mL), aqueous HCl (1 M, 20 mL) and aqueous NaOH (1 M, 20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give an orange oil. Trituration with ethyl ether gave N-(3'-carboethoxyphenyl)-2-